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β-Selective *C*-Glycosidations: Lewis-Acid Mediated Reactions of Carbohydrates with Silyl Ketene Acetals

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Abstract: *Several examples of β-selective C-glycosidation reactions, involving TMSOTf-promoted addition of sterically hindered silyl ketene acetals to glucosyl and galactosyl acetates, are presented.*
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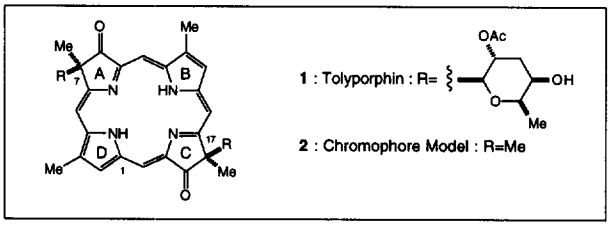
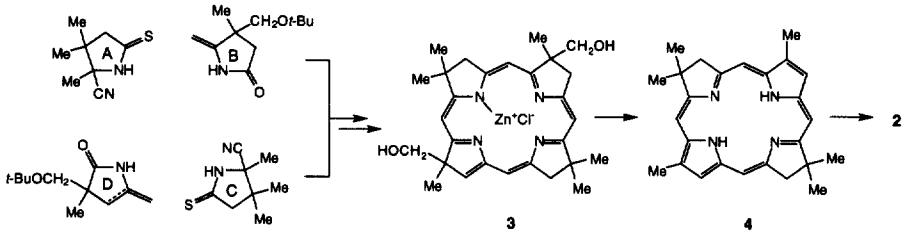
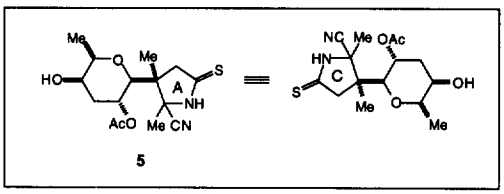
In the preceding paper[1] we reported the synthesis of a chromophore model **2** of the multidrug resistance reversing natural product tolyporphin (**1**). This synthesis contains two key transformations: (1) a double retroaldol/autoxidation reaction to convert an octahydroporphyrin **3** into a tetrahydroporphyrin **4**, and (2) a site-specific oxidation of **4** to the chromophore model **2**. The octahydroporphyrin **3** was synthesized from monocyclic precursors by using the Eschenmoser sulfide contraction/iminoester cyclization method. In order to extend this route to a synthesis of tolyporphin (**1**), we need to prepare thiolactam **5**, which corresponds to both ring A and ring C of the natural product. Thiolactam **5**, which can also be viewed as a *C*-glycoside,[2] contains two important structural characteristics: a β-oriented *C*-glycosidic bond and a quaternary center adjacent to the anomeric carbon.





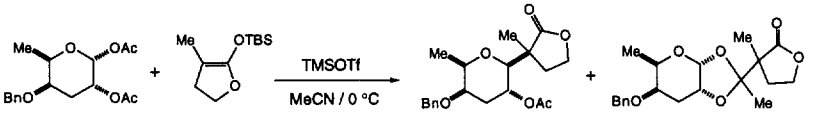


The utility of Lewis-acid promoted nucleophile addition to the anomeric center of carbohydrates for the synthesis of *C*-glycosides is well documented.[3-6] Due to the stereoelectronic effect, a nucleophile preferentially adds from an axial direction to the oxonium ion generated from a suitable carbohydrate derivative. As a result, α-*C*-glycosides are the predominant products from glycosidation with carbon nucleophiles, and β-*C*-glycosides are the products of hydride attack on ketols. An alternative synthesis of β-*C*-glycosides involves radical reduction of a C.1 methylthioketal.[7] In this communication, we wish to report a procedure for obtaining β-*C*-glycosides[8] from Lewis-acid mediated *C*-glycosidation of glycosyl-1-*O*-acetates with silyl ketene acetals.

In previous work from this laboratory, it was shown that $BF_3{\cdot}OEt_2$ promoted addition of allyltrimethylsilane (**N-1**) to 2,3,4,6-tetrabenzylglucose 1-*O*-acetate (**S-1**) or glucose pentaacetate (**S-2**) gave a 10:1 ratio of α- to β-allylglucopyrans (Table 1, entries 1 and 5).[4] However, we thought it might be possible to invert the stereochemical outcome of this process by adjusting electronic and/or steric properties of the nucleophile. In connection with the tolyporphin work, silyl ketene acetals (cf. **N-4**) seemed to be particularly attractive nucleophiles. Thus, we studied the efficiency and stereoselectivity of TMSOTf-promoted reactions of nucleophiles **N-2, N-3,** and **N-4** with substrates **S-1~S-4** .

As the results summarized in Table 1 indicate, the efficiency of carbon-carbon bond formation between silyl ketene acetals and carbohydrate C.1 acetates bearing a non-participating group at C.2 in the presence of Lewis acid is generally good (**S-1+ N-2~N-4** and **S-3 + N-2~N-4**). However, lower bond forming efficiency is observed for substrates with a participating group at C.2 (**S-1** series vs. **S-2** series and **S-3** series vs. **S-4** series). The poor yield of these latter cases can be attributed to the formation of a by-product arising from attack of the nucleophile at the carbonyl carbon of the C.2 acetate, exemplified by the production of **7** (Scheme 1).

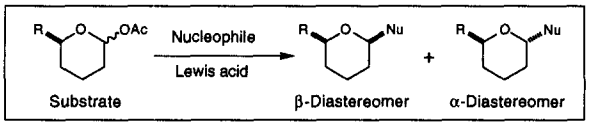
Scheme 1



S-4 **N-4** **6** (60% yield) **7** (35% yield)

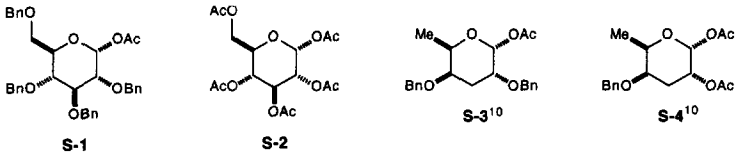
Compared with the widely recognized examples of α-selectivity in *C*-glycosidation, it is particularly pleasing to see the switch to β-selectivity observed with silyl ketene acetals as nucleophiles. Both γ,γ-disubstituted and unsubstituted silyl ketene acetals, which have heightened nucleophilicity relative to simple allylsilanes and enol ethers, display a preference for forming β-*C*-glycosides. In addition, increasing the steric bulk of the nucleophile at its reacting terminus[9] results in enhanced β-selectivity (**S-1 + N-2** vs. **S-1 + N-3** or **N-4** and **S-3 + N-2** vs. **S-3 + N-3** or **N-4**). Finally, β-selectivity is greatly increased by placing an acetate on the C.2 hydroxyl of the sugar (**S-2** series vs. **S-1** and **S-4** series vs. **S-3**). This effect is expected on the basis of the well-known neighboring-group participating ability of carbohydrate C.2 esters, and is consistent with the observation shown in Scheme 1.

Table 1



Entry	Substrate[a]	Nucleophile[b]	Stereoselectity (β:α)[c]	Yield[d] / Method[e]
1	**S-1**	**N-1**	<1:10	55% / A
2	"	**N-2**	1.4:1	57% / A
3	"	**N-3**	3:1	64% / A
4	"	**N-4**	3:1[f]	65% / A
5	**S-2**	**N-1**	<1:10	50% / B
6	"	**N-2**	>10:1	47% / B
7	"	**N-3**	>10:1	53% / B
8	"	**N-4**	---[g]	N.R. / B
9	**S-3**	**N-1**	<1:10	96% / A
10	"	**N-2**	1.1:1	72% / A
11	"	**N-3**	2:1	78% / A
12	"	**N-4**	8:1[f]	72% / A
13	**S-4**	**N-1**	<1:10	50% / A
14	"	**N-2**	>10:1	52% / A
15	"	**N-3**	>10:1	71% / A
16	"	**N-4**	>10:1[f]	60% / A

[a]The substrates used for this study were:



[b]The nucleophiles used for this study were:

[c]>10:1 ratios determined from ^{1}H NMR of purified anomer mixture. Otherwise, ratios determined by weight after preparative TLC separation of individual anomers. [d]combined yields of α- and β-anomers by preparative TLC. [e]Method A: To a 0.1 M solution of substrate in MeCN at 0 °C was added nucleophile (10 eq.) followed by TMSOTf (1 eq.). Method B: To a 0.1 M solution of substrate in MeCN at 0 °C was added nucleophile (10 eq.) followed by TMSOTf (1 eq.) and $BF_3{\cdot}OEt_2$ (9 eq.). [f]The major product was a ca.1.2:1 mixture of diastereomers at the α position. [g]No reaction; only starting material recovered.

In conclusion, this methodology should prove useful for the synthesis of β-*C*-glycosides and related compounds, and its application to a total synthesis of tolyporphin is in progress.

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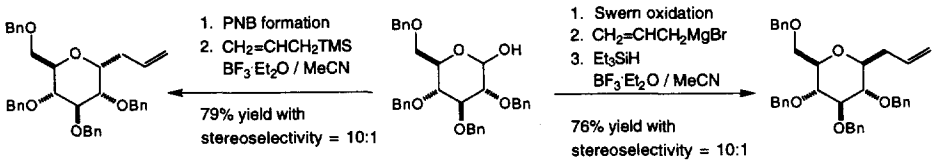
References and Notes.

1. Minehan, T. G.; Kishi, Y. preceding paper.

2. For a recent review on *C*-glycosides in general, see: Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*, Pergamon Press, Tarrytown, 1995.

3. For a recent review on *C*-glycoside synthesis in general, see: Postema, M. H. D. *C-Glycoside Synthesis*, CRC Press, Inc., Boca Raton, FL, 1995.

4. Lewis, M. D.; Cha, K; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. The examples shown below are representative in the terms of the efficiency and stereoselectivity of bond formation.



5. (a) Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289. (b) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281. (c) Schmidt, R. R.; Hoffman, M. *Tetrahedron Lett.* **1982**, *23*, 409. (d) Hosomi, A; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383.

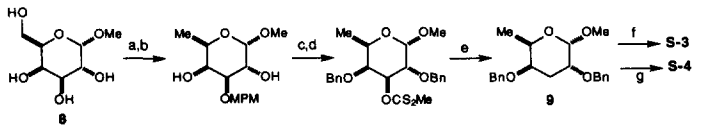
6. β-Selective *C*-allylation of carbohydrates bearing a C.2 phthalimido group is known: (a) Wei, A.; Haudrechy, A.; Audin, C.; Jun, H.-S.; Haudrechy-Bretel, N.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 2160. (b) Roe, B. A.; Boojamra, C. G.; Griggs, J. L.; Bertozzi, C. R. *J. Org. Chem.* **1996**, *61*, 6442.

7. Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504.

8. For a recent example of β-selective *C*-glycosidation by silyl ketene acetals, see: Smoliakova, I. P.; Caple, R.; Gregory, D.; Smit, W. A.; Shashkov, A. S.; Chizhov, O. S. *J. Org. Chem.* **1995**, *60*, 1221.

9. Attempted *C*-allylation of **S-1** and **S-2** with γ,γ-dimethylallytrimethylsilane gave a complex mixture of products, containing only minor amounts of the desired products.

10. These compounds were synthesized from methyl α-D-galactopyranose **8** by an 8 step sequence:



Reagents and Conditions:
(a) 1. Bu_2SnO (1 eq.), PhH-azeotrope, 8 h. 2. MPMBr (1 eq.), TBAI (1 eq.), 80 °C, 2.5 h; 52% overall yield. (b) 1. TsCl (1.1 eq.), Et_3N, DMAP, CH_2Cl_2. 2. $LiEt_3BH$ (5 eq.) or LAH (5 eq.), THF, r.t.; 60% overall yield. (c) NaH, imidazole, BnBr, TBAI, THF-DMF (4:1); 92% yield. (d) 1. DDQ (1.1 eq.), H_2O, CH_2Cl_2. 2. NaH, imidazole, CS_2, MeI, THF; 94% overall yield. (e) Bu_3SnH (10 eq.), AIBN, PhH; 50%. yield. (f) Ac_2O-AcOH (3:1), H_2SO_4 (0.1 eq); 80% yield. (g) Ac_2O, H_2SO_4 (0.1eq.); 55% yield.

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